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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/419,817	10/18/99	HUANG	X	03848.80923

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EXAMINER	
FORMAN, B	
ART UNIT	**PAPER NUMBER**
1655	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/419,817	Applicant(s) HUANG ET AL.	
	Examiner BJ Forman	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 23-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 23-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1 March 2001 has been entered.

The papers filed 1 December 2000 in Paper No. 8 in which claims 1 & 23 were amended is acknowledged. The amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 7 dated 11 September 2000 are withdrawn in view of the amendments and new ground for rejection. All of the arguments have been thoroughly reviewed but are deemed moot in view of the withdrawn rejections and new grounds for rejection. New grounds for rejection are discussed.

Applicant is reminded that changes to 37 C.F.R. § 1.121 require applicant to submit a clean set of all pending claims in addition to the marked up version of the amended claims.

Currently claims 1-16 & 23-38 are under prosecution.

Information Disclosure Statement

2. The information disclosure statement filed 7 February 2000 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but does not list the patents, publication, or other information submitted and therefore the information referred to therein has not been considered.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 2, 5, 7, 11-14, 16, 23, 24, 27, 29, 33-36 & 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Köster (U.S. Patent No. 6,197,498, filed 6 April 1999).

Regarding Claims 1 & 23, Vary et al. teach a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample (Column 2, lines 31-38), the method comprising amplifying a region of DNA comprising the polymorphic locus (Example 3, Column 12, lines 19-30 and primers PM and MM), wherein the primer comprises a 3' portion which is complementary to the region of DNA (Column 7, lines 23-26 and Fig. 3A) and a 5' portion which is complementary to all or part of a probe on a solid support and not complementary to the region of DNA (Column 7, lines 43-49), labeling the amplified DNA to form labeled amplified DNA products (Column 3, lines 54-60) and hybridizing the labeled DNA products to the probe on a solid support (Column 7, lines 43-49 and Fig. 3 A and B) and optionally detecting the labeled DNA products hybridized to the probe on the solid support to thereby detect a nucleic acid containing a polymorphic locus (Column 4, lines 53-56). Vary et al. do not teach the comprising a primer pair wherein the first primer comprises a 5' portion which is identical in sequence to all of a probe on a solid support. Köster teaches a similar method to determine a polymorphic locus comprising: amplifying a region of DNA comprising a polymorphic locus using a primer pair wherein the first primer of the pair terminates at its 3' end at the polymorphic locus, wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a

solid support and not complementary to the region of DNA to form a first strand and a second strand wherein the first strand comprises a portion identical to all or part of the probe and the second strand comprises a 5' portion complementary to all or part of the probe (Column 6, lines (Column 6, lines 53-62 and Fig. 4). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 5' portion of the primer being complementary to the capture-probe in the method of Vary et al. with the 5' portion being identical to the capture probe as taught by Köster to thereby immobilize the sense strand for the expected benefit detecting the presence of a polymorphism in the coding strand. Additionally, one skilled in the art would have been motivated to modify the single primer amplification of Vary et al. with primer pair amplification for the obvious benefit of exponential amplification of both strands of the target region.

Regarding Claims 2 & 24, Vary et al. teach the method wherein the labeling couples a labeled nucleotide to a 3' end (Column 3, lines 54-61).

Regarding Claims 5 & 27, Vary et al. teach the method wherein the nucleotide is radioactively labeled with ^{32}P-dATP (Column 3, lines 54-59).

Regarding Claims 7 & 29, Vary et al. teach the method wherein the nucleotide is epitopically labeled wherein the epitope is a halogen-modified nucleotide which is antibody-detected (Column 3, lines 63-65 and Column 4, line 66-Column 5, line2).

Regarding Claims 11 & 33, Vary et al. do not teach the method wherein two or more target sequences are detected simultaneously. However, Köster teaches the similar method wherein two or more target sequences are detected simultaneously wherein the target sequences are polymorphic loci (Column 4, lines 10-16 and 43-53). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single target detection method of Vary et al. with the detection of two or more targets as taught by Köster for the obvious benefit of economy of time and labor by multiplex detection and processing as taught by Köster (Column 4, liens 10-16).

Regarding Claims 12 & 34, Vary et al. does not teach the method wherein the sample comprises DNA from two or more individuals. Köster teaches the similar method wherein multiple samples are processed simultaneously (Column 4, lines 10-16) and it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made that the multiples samples of Köster encompasses sample from two or more individuals. Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the multiplex teaching of Köster to the method of Vary et al. and to analyze a sample comprising DNA from two or more individuals for the obvious benefit of economy of time and labor derived from multiplex assays and for the expected benefits of simultaneous detection and processing of multiple samples whereby samples can be compared and analyzed in comparison taught by Köster (Column 4, lines 10-16).

Regarding Claims 13 & 35, Vary et al. does not teach the method wherein two or more regions of DNA are amplified in a single reaction. Köster teaches the similar method wherein multiple samples are detected and processed simultaneously (Column 4, lines 10-16) and it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made that the multiplex processing of Köster encompasses detecting and processing two or more DNA regions. Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the multiplex teaching of Köster to the method of Vary et al. and to analyze two or more DNA regions in a single reaction, wherein each of the regions comprises a polymorphic locus for the obvious benefit of economy of time and labor derived from multiplex assays and for the expected benefits of simultaneous detection and processing of multiple polymorphisms as taught by Köster (Column 4, lines 10-16).

Regarding Claims 14 & 36, Vary et al. teach the method comprising a solid support (Column 4, lines 44-56) but they do not teach the solid support is a bead. Köster teaches the similar method wherein the solid support is beads (Column 12, lines 35-38).

Regarding Claims 16 & 38, Vary et al. teach the method comprising a solid support (Column 4, lines 44-56) but they do not teach the solid support is a high-density array. Köster teaches the similar method wherein the solid support is a high-density array i.e. DNA chip (Column 4, lines 12-16).

5. Claims 3-4, 8-10, 25-26 & 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Köster (U.S. Patent No. 6,197,498, filed 6 April 1999), Hames et al. (Nucleic Acid Hybridization: a practical approach, 1988, pages 35, 36 and 42-44) and Lapidus et al. (U.S. Patent No. 5,670,325, filed 14 August 1996).

Regarding Claims 3 & 25, Vary et al. teach a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample, the method comprising: amplifying a region of DNA comprising the polymorphic locus; labeling the amplified DNA to form labeled amplified DNA products; and hybridizing the labeled DNA products to the probe on a solid support (Column 7, lines 43-49 and Fig. 3 A and B) and optionally detecting the labeled DNA products hybridized to the probe on the solid support to thereby detect a nucleic acid containing a polymorphic locus (Column 4, lines 53-56) wherein labeling couples a labeled nucleotide to a 3' end (Column 3, lines 54-61). Köster teaches a similar method to determine a polymorphic locus further comprising: amplifying a region of DNA comprising a polymorphic locus using a primer pair wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support (Column 6, lines 53-62 and Fig. 4) but Vary et al. and Köster do not teach a terminal transferase catalyzes the step of labeling. However, it was known in the art that terminal transferase labels a 3' end specifically (see Hames et al. page 35-36). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify

the labeling of Köster et al. with the terminal transferase catalyzed labeling taught by Hames et al. for the known benefits of terminal transferase specificity as taught by Hames et al. (page 36, first full paragraph).

Regarding Claims 4 & 26, Vary et al. teach the method wherein the nucleotide is labeled (Column 3, lines 54-61) but they do not teach the nucleotide is fluorescently labeled. However, Lapidus et al. teach a similar method for determining the a nucleotide at a polymorphic locus comprising: amplifying a region of DNA using a primer wherein the primer terminates at its 3' end at the polymorphic locus wherein the primer comprises a 3' portion complementary to the region of DNA and labeling the amplified DNA wherein the labeling couples a labeled nucleotide to a 3' end (Column 6, lines 1-20) wherein the nucleotide is fluorescently labeled or radioactively labeled (Column 12, lines 28-31and Column 17, lines 6-18). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the radioactive label of Vary et al. with the fluorescent nucleotides of Lapidus et al. for the obvious benefits of eliminating the radioactive labels i.e. reduced hazard exposure and for the known benefits of fluorescent labels i.e. simple and fast detection.

Regarding Claims 8 & 30, Vary et al. teach the method further comprising detecting the label on the solid support (Column 4, lines 53-56) and Köster teach the similar method further comprising the step of detecting the label on the solid support (Fig. 4) but Vary et al. and Köster do not teach the label is fluorescent which is detecting optically. However, Lapidus et al. teach the similar method wherein the fluorescent label is detected optically (Column 18, lines 8-10). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the radioactive label and label detection of Vary et al. and Köster with the fluorescently labeled nucleotide and optical detection of Lapidus for the obvious benefits of eliminating the radioactive labels i.e. reduced hazard exposure and for the known benefits of fluorescent labels and fluorescent detection i.e. simple and fast detection.

Regarding Claims 9 & 31, Vary et al. do not teach the method wherein two pairs of primers are used. However, Köster teaches the similar method wherein two primer pairs are used wherein the first primer of each of the first and second pairs terminate at their 3' ends (Column 16, lines 17-39) in distinct nucleotides and wherein each 5' portion of each of said first primers is identical in sequence to all or part of a distinct probe at a known location on the support i.e. the target sequences are immobilized by hybridization between a portion of the target sequence and a capture nucleic acid molecule wherein the target sequences are arranged in a format that allows multiple simultaneous detections (Column 3, line 63-Column 4, line 1 and 10-16). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single primer of Vary et al. with the two primer pairs of Köster for the obvious benefit of economy of time and labor derived from multiplex assays and for the expected benefits of simultaneous detection and processing of multiple samples as taught by Köster (Column 4, lines 10-16).

Regarding Claims 10 & 32, Vary et al. do not teach the method wherein quantities of fluorescent label at known locations on a solid support are detected. Köster teaches the similar method wherein the different allelic forms of the polymorphic locus are detected (Column 16, lines 26-32) and wherein they are positioned at known locations on the solid support (Column 3, line 63-Column 4, line 1 and 10-16) but they do not teach quantities of fluorescent label at known locations on the solid support are compared. However, Lapidus et al. teach the similar method wherein the quantities of fluorescent label are compared to thereby determine a ratio of nucleotides at the polymorphic locus i.e. homozygous or heterozygous (Column 18, lines 3-33). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify radioactive polymorphism detection of Vary et al. and position-specific polymorphism detection of Köster with the fluorescent polymorphism detection of Lapidus et al. wherein fluorescent labeled polymorphism are detected to determine a ratio of polymorphic loci for the obvious benefit of eliminating the radioactive detection of Vary et al. (i.e. decreased

hazard) and for the expected benefit of accurately determining heterozygosity as taught by Lapidus et al. (Column 18, lines 3-10).

Claims 6 & 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Köster (U.S. Patent No. 6,197,498, filed 6 April 1999) and Mullan (U.S. Patent No. 5,455,169, filed 4 June 1992).

Regarding Claims 6 & 28, Vary et al. teach a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample, the method comprising: amplifying a region of DNA comprising the polymorphic locus; labeling the amplified DNA to form labeled amplified DNA products; and hybridizing the labeled DNA products to the probe on a solid support (Column 7, lines 43-49 and Fig. 3 A and B) and optionally detecting the labeled DNA products hybridized to the probe on the solid support (Column 4, lines 44-56) to thereby detect a nucleic acid containing a polymorphic locus (Column 4, lines 53-56). Köster teaches a similar method to determine a polymorphic locus further comprising: amplifying a region of DNA comprising a polymorphic locus using a primer pair wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support (Column 6, lines 53-62 and Fig. 4) but Vary et al. and Köster do not teach the nucleotide is enzymatically labeled. However, enzymatic labels were well known and routinely practiced in the art at the time the claimed invention was made as taught by Mullan who teach a method of detecting a polymorphism comprising labeling amplified DNA (Column 10, lines 20-39) wherein the nucleotide is enzymatically labeled (Column 8, lines 33-39). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the label of Vary et al. and Köster with routinely practiced enzymatic labeling based on available reagents and equipment for the obvious benefit of economy of reagents and equipment and for the known benefits of eliminating the radioactive label.

6. Claims 15 & 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Köster (U.S. Patent No. 6,197,498, filed 6 April 1999) and Lockhart et al (U.S. Patent No. 5,556,752).

Regarding Claim 15, Vary et al. teach a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample, the method comprising: amplifying a region of DNA comprising the polymorphic locus; labeling the amplified DNA to form labeled amplified DNA products; and hybridizing the labeled DNA products to the probe on a solid support (Column 7, lines 43-49 and Fig. 3 A and B) and optionally detecting the labeled DNA products hybridized to the probe on the solid support (Column 4, lines 44-56) to thereby detect a nucleic acid containing a polymorphic locus (Column 4, lines 53-56). but they do not teach the solid support is a microtiter dish. Köster teaches a similar method to determine a polymorphic locus further comprising: amplifying a region of DNA comprising a polymorphic locus using a primer pair wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support (Column 6, lines 53-62 and Fig. 4) wherein the solid support is a bead (Column 12, lines 35-38) and a high density array i.e. DNA chip (Column 4, lines 12-16) but Vary et al. and Köster do not teach the support is a microtiter dish. However, microtiter dish solid supports were well known and routinely practiced in the art at the time the claimed invention was made as taught by Lockhart et al. who teach a nucleotide detection method wherein probes are immobilized on a solid support wherein the support is beads (Column 7, lines 27-33) and microtiter dishes (i.e. a polystyrene support having depressed regions) (Column 8, lines 41-44 and 50). It would have It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the solid support of Vary et al. with the microtiter support of Lockhart et al. for the expected benefit simplifying polymorphism identification by immobilizing probes in regionally defined and separate areas to thereby identify polymorphism based on the region of hybridization.

Conclusion

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
March 22, 2001

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